REMARKS

Claims 1-19 were rejected under 35 U.S.C. § 103(a) over Merck & Co., Inc. (GB Patent No. 947,643) in view of Kijima et al (US 4,061,660), Kijima et al (US 4,039,573) and Morita et al (US 4,163,664). New independent Claim 20 has been added.

Examiner acknowledges that the applicants show how the cited references differ from the instant invention, but contend that the obviousness test under 35 U.S.C. 103 is whether the invention would have been obvious in view of the prior art taken as a whole, citing In re Metcalf et al, 157 U.S.P.Q. 423. The Examiner insists that it would have been obvious to a person of ordinary skill in the art at the time of the invention was made to use the teachings of the cited secondary references, with a reasonable expectation of success, for washing crystals or an oily form of reduced coenzyme Q_{10} because it is within the scope of the art to optimize the conditions and achieve the claimed results through routine experimentation according to the Examiner. The applicants steadfastly disagree with the Examiner's conclusion.

According to the invention of Claims 1-20, reduced coenzyme Q_{10} is purified by washing crystals and/or oil of reduced coenzyme Q_{10} with a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water and thereby removing a water-soluble impurity, i.e., a reducing agent and an impurity derived from a reducing agent. In large-scale production, it is essential to conduct a simple and easy purification of the product. Therefore, purification without the use of column chromatography is commercially very desirable. The applicants invention enables such purification by utilizing a water-soluble organic solvent step alone.

Regarding the references relied upon in the 35 U.S.C. § 103(a) rejection, Merck & Co. teaches to prepare a reduced form of coenzyme Q_{10} by reducing an oxidized form of coenzyme Q_{10} with sodium borohydride. Merck & Co. also teaches that the pure reduced form of coenzyme Q_{10} may be recrystallized. However, Merck & Co. is silent about the fact that the product obtained has problem specific to the reduced form of coenzyme Q_{10}. Specifically, the Merck & Co. product necessarily

contains water-soluble impurities, particularly the reducing agent and/or impurities derived from the reducing agent, and it is difficult to remove them (see page 1, line 33 to page 2 line 9 of the applicant's specification). In addition to this, Merck & Co. does not even imply washing of crystals.

Regarding the secondary references, the Examiner cites Example 1 of Kijima et al. (US 4,061,660), Example 3 of Kijima et al. (US 4,039,573) and Example 1 of Morita et al. The teaching of each of these references has nothing to do with the present invention, however. First of all, these supporting references do not teach synthesizing the reduced form of coenzyme Q_{10}. Furthermore, they do not teach use of a reducing agent.

In Example 1 of Kijima et al. ('660) and Example 1 of Morita et al., 2-methyl-3-decaprenyl-4, 5, 6-trimethoxyphenol is prepared, but it is not the reduced form of coenzyme Q_{10}. Furthermore, a reducing agent is not used in the preparation procedure. Accordingly, the product, 2-methyl-3-decaprenyl-4, 5, 6-trimethoxyphenol, does not have the problem of impurities which are caused by the reducing agent.

In Example 3 of Kijima et al. ('573), it is the reduced form of coenzyme Q_9 that is prepared, not coenzyme Q_{10}. Further, the reduced form of coenzyme Q_9 is obtained by reacting 2, 3-dimethoxy-5-methyl-1, 4-benzohydroquione-4monoacetate with solanesol without using a reducing agent. That product does not contain impurities caused by the reducing agent and is subjected to the oxidation reaction without purification.

In Example 1 of Kijima et al. ('660), the reaction mixture contained silica-alumina (see col. 4, lines 40 to 43). The filtration was carried out to remove the solid material, namely silica-alumina. After the filtration, the filtered solids, namely silica-alumina, were washed with diethyl ether to collect a desired product which adhered to the surface of silica-alumina and to increase the yield. Such washing is a common procedure, and a person skilled in the art would easily understand that the procedure is not used for removing impurities from crystals of a desired product.

After the washing, the filtrate and the washing liquor were collected, washed with water and then with aqueous solution of sodium hydroxide, and concentrated to

obtain a light yellow oily product. The crude product was purified by silica gel column chromatography (see col. 4, lines 51 to 59). The reference explicitly teaches that the filtrate was washed with water, and the purification of the crude product was carried out by column chromatography. The procedure does not at all include a washing of crystals or oil of a desired product with a water-soluble organic solvent.

In Example 1 of Morita et al., the reaction mixture was filtered, and the filtrate was washed with methanolic aqueous sodium hydroxide solution and then with aqueous methanol solution (see col, 4, lines 30 to 36). The procedure is for washing of filtrate liquor, namely a solution of a desired product. The reference does not at all teach a washing of crystals or oil of a desired product with a water-soluble organic solvent.

In Example 3 of Kijima et al. ('573), the reaction mixture was filtered, and the filtrate was washed with water and then with a weak-caustic soda aqueous solution. Later, the ether portion was washed with water and then with saline solution. The procedure does not at all include a washing of crystals or oil of a desired product with a water-soluble organic solvent.

As discussed above, the secondary references do not teach washing crystals or oily form of the product with a water-soluble organic solvent or a mixture of a water-soluble organic solvent and water. Accordingly, Merck & Co. does not present a legally proper foundation for the 35 U.S.C. § 103(a) rejection and the allegedly supporting references provide no legally proper support!

Turning now to the unexpected effects of the applicants' invention, according to the claimed invention, reduced coenzyme Q_{10} is purified by washing crystals and/or oil of reduced coenzyme Q_{10} with a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water. A water-soluble impurity, i.e., a reducing agent and an impurity derived from a reducing agent is thereby removed. In large-scale production, it is essential to conduct a simple and easy purification of the product. Therefore, purification without column chromatography is highly desirable. The present invention enables such a purification by utilizing a water-soluble organic solvent alone!

The Examiner says that it is desirable to use suitable solvents in which impurities get dissolved, and the selection of a solvent depends on the solubility of the impurities. In this regard, it would seem normal to use water for washing in order to remove water-soluble impurities from reduced coenzyme Q_{10} crystals which are highly insoluble to water. However, Table 1, for example, in the applicants' specification shows that the results would be contrary to those expected.

In Example 1, crystals of reduced coenzyme Q_{10} (containing 3.2% of L-ascorbic acid and 0.36% of oxalic acid) obtained in Production Example 1 were each washed with aqueous ethanol solutions (mixtures of ethanol and water). As shown in Table 1, after washing contents of L-asorbic acid were 0.07% or less and contents of oxalic acid were 0.05% or less. On the other hand, in Comparative Example 1 where water was used for washing, content of L-ascorbic acid was 0.18% and content of oxalic acid was 0.15%, and recovery percentage was only 97%.

It should be noted that the reduced coenzyme Q_{10} has poor wettability against water (page 2, lines 24 to 25 of the specification). If water is used to wash crystals and/or oil of reduced coenzyme Q_{10}, a sufficient amount of water cannot arrive at impurities existing between crystals and/or oily portions. Therefore, impurities cannot be removed sufficiently. Furthermore, it is troublesome to carry out the discharge operation.

As discussed above, the cited references neither teach the purification method according to the present invention nor understand problems specific to reduced coenzyme Q_{10}. The secondary references do not even teach synthesizing the reduced coenzyme Q_{10} or the use of a reducing agent. Therefore, it would not be predicted from the cited references, either alone or in combination, that a water-soluble organic solvent is most effective for removing water-soluble impurities and for carrying out a simple and easy purification in purification of reduced coenzyme Q_{10}. Accordingly, applicants submit that the present invention would not be rendered obvious based on the teaching of Merck & Co. in combination with Kijima et al. ('660) and Kijima et al. ('573) or Morita et al.

Respectfully submitted,

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